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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/061,019	04/15/1998	KATHERINE H. KODAMA	GC272D2	1225

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GENENCOR INTERNATIONAL, INC.
ATTENTION: LEGAL DEPARTMENT
925 PAGE MILL ROAD
PALO ALTO, CA 94304

EXAMINER

RAO, MANJUNATH N

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 10/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/061,019

Applicant(s)

KODAMA ET AL.

Examiner

Manjunath N. Rao, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 July 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 11-18 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 11-18 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application (PTO-152)
- ☐ Other: _____

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DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7-21-04 has been entered.

Claims 11-18 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 7-21-04, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawlis (a) et al. (US 5,679,543, issued 10-21-1997, filed 10-5-1994) or Lawlis (b) et al. (US 6,130,063, issued 10-10-2000, filed 10-5-1994) and Kitagawa et al. (BBRC, 1993, Vol. 194(1):375-382.).

Claims 11-18 are drawn to a fusion polypeptide wherein the polypeptide comprises from the N-

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terminal side a signal peptide functional in *Aspergillus*, a secreted polypeptide or a portion thereof secreted from *Aspergillus* sp., an optional cleavable linker sequence followed by a glycosyltransferase having a deletion of the transmembrane anchor domain, wherein the glycosyltransferase is selected from sialyltransferase, galactosyltransferase or fucosyltransferase and wherein the signal peptide sequence is selected from the signal peptides of glucoamylase, α -amylase etc., wherein the secreted polypeptide comprises either full length or portion of glucoamylase from *Aspergillus niger* var. *awamori*.

Lawlis(a) et al. or Lawlis (b) et al. teach a fusion protein comprising a signal peptide and a secreted polypeptide or portion thereof from *Aspergillus* sp. such as *A.niger* and *A.awamori*, further comprising a cleavable linker region and any desired polypeptide sequence which when expressed in a fungal host cell such as *A.niger* and *A.awamori*, is expressed at an increased level when compared to a fungal cell expressing such a heterologous polypeptide that is not fused to a secreted *Aspergillus* polypeptide. The reference teaches that the increase in expression is significant such that it can be used for large scale production of heterologous proteins. However, the reference does not specifically teach a fusion polypeptide comprising a glycosyltransferase in which the membrane anchor domain has been deleted as a heterologous polypeptide.

Kitagawa et al. teach the cloning and expression of a human sialyltransferase lacking the first 60 amino acids comprising the membrane anchor region in order to express said enzyme in a soluble form. In fact the reference teaches the expression of the enzyme as fusion protein comprising the human insulin signal sequence in the place of the signal peptide in the instant invention and comprising protein A in place of the secreted *Aspergillus* polypeptide in the instant

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invention. The reference teaches that such expression provides the sialyltransferase as a soluble protein which can be used for *in vitro* sialylation experiments.

With the above two references in hand, it would have been obvious to one of ordinary skill in the art to make a fusion protein as taught by Lawlis et al. using the sialyltransferase polypeptide lacking the membrane anchor domain taught by Kitagawa et al. in place of the fourth polypeptide sequence or the desired polypeptide position in the Lawlis et al. invention. It would also be within the knowledge of those skilled in the art to delete the membrane anchor domain from the sialyltransferase because retaining such a sequence would clearly hamper the secretion of the heterologous polypeptide because of the anchoring domain. Furthermore, judging from a literature survey it appears that such knowledge (i.e., deletion of the transmembrane anchor domain from glycosyltransferases to produce soluble form of the enzyme) was common in the art. One of ordinary skill in the art would have been motivated to do so as sialyltransferases have been known in the art to play an important role in glycosylation of recombinant polypeptides and are used for *in vitro* glycosylation purposes with more demand for pure enzyme and Lawlis et al. teach that expressing heterologous polypeptides as fusion polypeptides according to their teachings increases the yield of the heterologous polypeptide. One of ordinary skill in the art would have a reasonable expectation of success because Lawlis et al. provide methods for making such a polypeptide in general and Kitagawa et al. provide a glycosyltransferase lacking the transmembrane anchor domain.

Therefore, the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

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In response to the previous Office action, applicants continue to traverse the above rejection arguing that Lawlis et al. fails to teach or suggest a fusion polypeptide that is encompassed by the presently amended claims and that it fails to teach that a normally membrane bound enzyme such as a glycosyltransferase can be secreted and that a truncated gene is suitable for expression in an integration plasmid. Examiner respectfully disagrees with the applicant that Lawlis et al. reference must teach such a limitation (normally membrane bound). This is because, instant claims do not have above limitations. Lawlis et al. teach that any desired polypeptide can be used in their fusion polypeptide which encompasses even the glycosyltransferases that may or may not be membrane bound.

Applicant next argues that Lawlis et al. fails to teach or suggest that a truncated gene or a gene encoding a membrane bound protein is compatible with DNA construct contemplated therein and that Lawlis et al. enumerates "desired polypeptides" none of which include a membrane-bound or truncated protein and therefore skilled artisan would not upon reading the above reference conclude that membrane-bound or truncated proteins were contemplated therein. First of all, the Lawlis et al. reference is not limited only to the exemplified proteins. While a glycosyltransferase may not be included in the examples, such a protein is still encompassed under "desired proteins". Nowhere Lawlis et al. teach or suggest that glycosyltransferases whether membrane bound or truncated are not suitable for use in the fusion polypeptide. That said, contrary to applicant's argument, those skilled in the art will not conclude that the method of making fusion polypeptide taught by Lawlis et al. cannot be applied for glycosyltransferases. Furthermore, Examiner reiterates that instant claims are not limited to such proteins either.

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Next, applicant's argument that there is no teaching in Lawlis et al. (a or b) that a truncated version of the desired protein would result in a functional protein being expressed and secreted when fused to a secreted protein native to *Aspergillus* and that linking the truncated protein to another protein may result in an incorrectly folded protein or a protein that is subject to incorrect/improper processing is all highly misplaced and instant claims do not have all such limitations. All limitation in the instant claims concern the first and second proteins, which the above references satisfy those limitations.

Applicant next argues at length regarding the reference of Kitagawa et al. Examiner finds that such arguments are highly misplaced as his rejection was not based on such teachings of Kitagawa et al. Furthermore, it is also not clear to the Examiner as to why Kitagawa et al. reference must teach that other expression systems could be used to express glycosyltransferases generally or that the expression constructs used in their studies could be transferred to other host cells etc.? Examiner is not arguing that the entire construct provided by Kitagawa et al. can be used in an *Aspergillus* host cell. Examiner has mainly used the reference to show the availability of a glycosyltransferase lacking membrane anchor domain and the reason/use for making such deletions. Examiner would like to remind the applicant that the above rejection is an obviousness type rejection and that each of the reference need not teach each and every limitation of the claims and that it is the combination of the references that should meet the limitation of the claims. That said, Examiner reiterates the Kitagawa et al. specifically teach a glycosyltransferase lacking the membrane anchor region. The reference also teaches that by deleting such region the glycosyltransferase can be produced in a soluble form.

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Applicant continues a tangential argument that there is “no suggestion in Kitagawa et al. reference for the use of the vector for commercial quantities of the enzyme in a fungal host or expression system..... thus, taken as a whole as the Examiner is required to do, one of skill in the art would read the Kitagawa reference...”. Examiner respectfully disagrees with such line of argument. As reiterated above Examiner has mainly used the reference to show the availability of a glycosyltransferase lacking membrane anchor domain and the reason/use for making such deletions and all the remaining motivation and expectation of success have been derived from Lawlis et al. references.

With regard to Kitagawa et al. reference applicant again argues that Examiner has ignored the fact that the transfer of an expression cassette useful in one host system is not transferable to another etc. Examiner respectfully disagrees with such argument. This is because Examiner has not argued in his rejection that it would be obvious to those skilled in the art to simply take the entire construct provided by Kitagawa et al. and place it in an *Aspergillus* host cell. Applicant next argues that there is no teaching in the reference that the truncated gene if fused to another protein or fragment thereof with yet another different signal sequence in yet another host system that it would function properly. Examiner respectfully disagrees with such an argument. Kitagawa et al. have exactly taught the same i.e., a normally membrane bound glycosyltransferase devoid of its anchor domain linked to another signal peptide (here insulin) and fused to another polypeptide is secreted as a soluble protein in an entirely different host cell. Applicant argues that the only reason the active enzyme is secreted is due to the presence of protein A. Such an argument is irrelevant to the instant situation. This is because, as stated above, Examiner has used the reference to show the availability of a glycosyltransferase lacking

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membrane anchor domain and the reason/use for making such deletion. Contrary to applicant's argument it would be well within the reach of those skilled in the art to conclude that the glycosyltransferase in the Kitagawa et al. reference can be secreted without its signal peptide if linked to another appropriate signal peptide. Such a teaching is generally well understood in the art and can even be stated as common knowledge in the art.

Applicant continues at length several lines of argument that there is no motivation, and that at best it would be "obvious to try" etc. However, Examiner respectfully disagrees with such arguments because he has clearly stated that reasons for motivation and a reasonable expectation of success. Therefore for all the above reasons, Examiner continues to maintain that the combination of the above references would have rendered the above invention would have been *prima facie* obvious to those skilled in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 11-18 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 17-26 of U.S. Patent No. 5,679,543 or claims

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17-26 of US 6,130,063 and in view of Kitagawa et al. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim, because the examined claim is either anticipated by, or would have been obvious over the reference claim. See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 11-18 of the instant application are directed to fusion polypeptide comprising from the N-terminal a first, second, third and fourth sequence wherein the first sequence comprises signal peptide functional in *Aspergillus* and the second sequence comprises polypeptide secreted from *Aspergillus*, such as glucoamylase, followed by a third (optional) and fourth sequence comprising a cleavable linker polypeptide and a glycosyltransferase polypeptide without its membrane anchor domain. Claims 17-26 of both the reference patents while not totally identical to the instant claims are also directed to fusion polypeptide comprising from the N-terminal a first, second, third and fourth DNA sequence wherein the first and second sequences encode *Aspergillus* signal peptide and a polypeptide that can be secreted by *Aspergillus*, such as the glucoamylase followed by a third and fourth sequences comprising a cleavable linker polypeptide and the sequence of any desired polypeptide, which encompasses the polypeptide sequence of glycosyltransferase as claimed in the instant claims.

The inventions claimed in the instant application and in the reference patent are similar to one another. The portion of the specification (and the claims) in the reference patents, while broader than the claims in the instant application, includes several embodiments that would

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anticipate the invention claimed in the instant application. Claims of the instant application listed above cannot be considered patentably distinct over claims 17-26 of the reference patents when there is specifically recited embodiments that would either anticipate mainly claims 11-18 of the instant application or alternatively render them obvious. Alternatively, claims 11-18 cannot be considered patentably distinct over claims 17-26 of the reference patents when there is specifically disclosed embodiment in the instant application that falls within the scope of claims 17-26 of the reference patents because it would have been obvious to one having ordinary skill in the art to combine the teachings of the patent with that of Kitagawa et al. and slightly modify claims 17-26 of the reference patents by selecting a specifically disclosed embodiment that supports those claims i.e., a fusion protein sequence comprising all the subsequences of those taught in the reference patents except for the last sequence now limited to a glycosyltransferase lacking the transmembrane anchor domain. One of ordinary skill in the art would have been motivated to do this because the reference patents teach that the yields of heterologous polypeptides are higher when compared to other methods of expressing heterologous polypeptide and Kitagawa et al. reference teaches that recombinant sialyltransferase can be obtained in the soluble form when expressed without transmembrane anchor domain as a fusion protein.

Conclusion

None of the claims are allowed.

This is a continuation (RCE) of applicant's earlier Application No. 09/061,019. All claims are drawn to the same invention claimed in the earlier application and could have been

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finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306/9307 for regular communications and for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.
Primary Examiner
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October 4, 2004